REMARKS

Claims 1-13 are pending in the application. Claims 1, 5, 9 and 13 are amended. Claim 1 was amended to follow the same format as claim 5 for easy comparison. Well-known transitional phrase of differing scope are used in claims 1 and 5, namely "comprising" and "consisting essentially of"; see MPEP 2111.03.

Paragraph [[0020]] of U.S. published application no. 2007/0065493 A1 (the publication of the present application) supports the addition of consisting of polybutene and/or liquid paraffin as follows:

---- "Examples of the softener include paraffin-based oils, silicon oils, higher fatty acids, vegetable oils and polybutenes. Of these, liquid paraffins are particularly preferred." ----

Claim Rejections – 35 USC § 112

Claims 1-13 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that she was unable to locate support for the exclusion of alcohol. Applicants respectfully maintain that the application does support the absence of alcohols in paragraphs [0005] and [0011] of the U.S. published application no. 2007/0065493 A1, which is the publication corresponding to present application.

Paragraph [0005] states:

"One example is a reservoir-type preparation in which estradiol is dissolved in a gel made of hydroxypropyl cellulose and ethanol. … However, since these preparations contain a volatile ingredient [ethanol], there is a fear that drug releasability is changed. In addition, contained ethanol is irritant to the skin, frequently causing rubor where the preparation is applied to the skin." (Emphasis added.)

Paragraph [0011] states:

"In view of the aforementioned problems, it is an object of the present invention to provide an external patch can ensure high transdermal absorption of estrogen and/or progestogen and have little irritancy to the skin." (Emphasis added.)

Test Example 4, paragraphs [0043-45] tests patches made according to the application against "commercial product B" ("a reservoir-type patch in which the hormone is dissolved in ethanol"). As shown in table 4, the patches made in accordance with the application created minor erythema an hour after removal and almost no irritation 24 hours after removal, while commercial product B, with alcohol, caused erythema and edema an hour after removal, and erythema remained even 24 hours after removal.

Someone skilled in the art would understand that one of advantages taught of the patches of application is avoiding the problem of alcohol by providing a patch that is effective without alcohol, an irritant. If the examiner thinks different language would better reflect the teaching of the application on this point, applicants would certainly consider any suggestions.

Claim Rejections – 35 USC § 103

Feature of the present disclosure

The present application relates to an external patch comprising a backing and an adhesive layer laminated onto the backing, the adhesive layer containing as essential components a 5 to 50 wt% styrene-isoprene-styrene block copolymer (SIS), a 20 to 70 wt% rosin-based resin, a 10 to 60 wt% softener consisting of polybutene and/or liquid paraffin, and a 1 to 20 wt% polyvinylpyrrolidone, along with estrogen and/or progestogen as active ingredients, and the adhesive layer being free from any alcohol.

The adhesive base material of the external patch contains the rosin-based resin as adhesive resin and thereby the crystallization of progestogen in the patch base material is reduced. That is, the rosin-based resin is used for dissolving progestogen and for preventing the crystallization of progestogen in adhesive base material.

Further, polyvinylpyrrolidone is used for dissolving estrogen, and is used for preventing the crystallization of estrogen in adhesive base material. In the pharmaceutical field, polyvinylpyrrolidone is commonly used as binding agent or suspending agent.

Therefore, the present application also shows that the adhesive base material of the external patch contains, along with SIS, the rosin-based resin as an adhesive resin, and polyvinylpyrrolidone, the softener consisting of polybutene and/or liquid paraffin for dissolving estrogen and/or progestogen and improving the following ability of the patch with the irregularities of the skin surface. Thus the crystallization of the drug in the base material is reduced in the external patch of the present application, and furthermore, the external patch ensures stable drug release while causing little irritancy to the skin.

These advantages are not taught by the cited prior art and are well demonstrated in the Examples of the present specification (Please refer to Tables 3 & 4, and Figures 1 & 2).

Furthermore, the adhesive layer of the present invention does not contain alcohol material as an absorption enhancer (sorbefacient), typically ethanol, and therefore, the external patch of the present invention can ensure stable drug release and transdermal drug absorption without irritation of the skin as shown in Example 4.

Claims 1-13 were rejected under 35 U.S.C. §103(a) as being unpatentable or Maki et al. (US 2004/0039356) in view of Hirano et al. (JP 11-001441).

The Examiner pointed out that Maki discloses a composition for external preparation used for hormone, such as 17-B-estradiol or norethisterone acetate replacement therapy. The adhesive of Maki comprises:

polyvinylpyrrolidone in the amount of 1-10% by mass,
vegetable oils, which are softeners, in the amount of 1-25% by mass,
rubber polymers, including SIS copolymer, and
hydrogenated rosin glycerin ester resins.

Maki does not disclose the amount of the SIS copolymer to be used. The thickness of the layers are not disclosed, however, the examiner maintains it would have been obvious to one ordinary skill in the art at the time the invention was made to have prepared a film in varying thicknesses based on the needs of the patch.

Hirano discloses a percutaneous absorption patch comprising;

a. 10-30% of SIS copolymer;
b. 10-60% of a softening agent;
c. 20-60% of tackifying resin.

The medicinal ingredient is an estrogen or progesterone.

Thus, the Examiner concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the amount of the SIS copolymer disclosed by Hirano into the adhesive disclosed by Maki since both references are drawn to drug in adhesive composition comprising SIS, softening agent, and tackifying resins.

However, Maki relates to a composition for external preparations, which contains vegetable oil and polyvinylpyrrolidone as a sorbefacient and/or a dissolution aid. In the external preparation of Maki, the combination of vegetable oil and polyvinylpyrrolidone is effective for promoting the percutaneous absorption of pharmaceutical ingredients and for relieving skin irritation. Therefore, the feature of the external preparation of Maki is using vegetable oil and polyvinylpyrrolidone at the same time, and thus polyvinylpyrrolidone is not used alone as sorbefacient and/or a dissolution aid.

Further, in the external preparation of Maki, when a substrate component selected from acrylic polymers or rubber polymers is combined with a composition component comprising vegetable oil and polyvinylpyrrolidone, the adhesive preparation having the advantage of good skin permeability of pharmaceutical ingredients and relieved skin irritation can be obtained. Thus, in the external preparation of Maki, the combination of vegetable oil and polyvinylpyrrolidone is essential feature.

Maki et al. neither describe nor suggest a rosin-based resin act as effectively solubilizing agent for progesterone, and certainly do require the amount of rosin-based resin disclosed and claimed by applicants. In the Example 1 of Maki, only 5.0% by mass of hydrogenated rosin glycerin ester was used for 8.0 wt by mass of norethisterone acetate.

On the contrary, in the present invention 20 to 70 wt% of the rosin-based resin was used for the 1 to 10 wt% of progesterone, and thus, the amount of the rosin-based resin of the present invention is greater than the amount of Maki preparation, and in Maki, there is no idea of using the rosin-based resin as the solubilizing agent for progesterone.

In the external patch taught by applicants, the adhesive layer of the present invention does not contain alcoholic material as an absorption enhancer (sorbefacient), such as ethanol or hexylene glycol, in order to prevent the skin irritation.

Furthermore, vegetable oil is not used in the present invention, and only SIS copolymer, the rosin-based resin, the softener consisting of polybutene and/or liquid paraffin, and the polyvinylpyrrolidone are essential component of the adhesive layer of the present invention. Therefore, the external patch of the present invention is clearly different from that of Maki preparation.

The secondary reference, Hirano et al., relates to a percutaneously absorbable preparation characterized in that the said preparation uses a styrene-isoprene-styrene block copolymer (SIS), a softener, a tackifying resin and hexylene glycol as the ingredients for the substrate composition for percutaneous absorption whereby solubility and skin permeation of the pharmaceuticals are possible and a predetermined amount of the pharmaceutical can be correctly and surely administered to patients.

The specific feature of the invention of Hirano is using of hexylene glycol, i.e., polyalcohols, as an absorption accelerating agent and/or a solubilizer for a pharmaceutical ingredient. Hexylene glycol has been known to be used as moisturizer and an antibacterial agent as cosmetic materials; however, in the invention of Hirano, this hexylene glycol is used as an absorption accelerating agent and/or a solubilizer for a pharmaceutical ingredient. Therefore, in Hirano, hexylene glycol has to be used as one of the essential components. See paragraphs [0013] and [0014] of Hirano. The preparation disclosed in the Hirano reference would not even be an attractive starting material for experimentation, since hexylene glycol is a diol and like another alcohol, ethanol, is an irritant as discussed above. One of the advantages of the preparation of the present application is reduced skin irritation as shown in Table 4. See paragraphs [0044] and [0045] of published application.

In the Office Action, the Examiner noted that Maki does not disclose the amount of the SIS copolymer to be used; however, the examiner argues it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the amount of the SIS copolymer disclosed by Hirano into the adhesive disclosed by Maki since both references are drawn to drug in adhesive composition comprising SIS, softening agent, and tackifying resins.

However, Hirano requires hexylene glycol to be an essential component, and the amounts of other components were determined based on the amount of hexylene glycol.

For example, in Hirano, there are the following descriptions:

- - - Hexylene glycol can be used within such a range that it does not substantially dissolve the ingredients of the substrate composition, particularly SIS copolymer or that a substantial dissolution is not noted and, therefore, good cohesive force and stability can be achieved. - - -

(Paragraph [0019] of EP 0976405 A1, which is correspond to Hirano JP 11-001441)

- - - Tackifying resin has an appropriate tackiness and an inter miscibility with hexylene glycol within the above-mentioned range. If the tackifying resin is outside of the above range, sufficient compounding of hexylene glycol and a sufficient absorption accelerating effect by hexylglycol are not achieved. - - -

(Paragraph [0020] of EP 0976405 A1, which is correspond to Hirano JP 11-001441)

As mentioned above, in Hirano, hexylene glycol, i.e., polyalcohol, has to be used as one of the essential components, and the amount of other components were determine based on the amount of hexylene glycol.

While for Maki, the combination of vegetable oil and polyvinylpyrrolidone is effective for promoting the percutaneous absorption of pharmaceutical ingredients and for relieving skin irritation without using hexylene glycol, i.e., polyalcohol.

A feature of the present invention is that the adhesive base material of the external patch contains the rosin-based resin as adhesive resin and thereby the crystallization of progestogen in the patch base material is reduced. That is, the rosin-based resin is used for dissolving progestogen and for preventing the crystallization of progestogen in adhesive base material.

Further, polyvinylpyrrolidone is used for dissolving estrogen, and is used for preventing the crystallization of estrogen in adhesive base material, and the external patch of the present invention ensures stable drug release and cause little irritancy to the skin.

Applicants respectfully submit that there is no suggestion of all the elements in the claims of the present invention, as amended and currently pending, in the prior art references and no reason why a person of ordinary skill would combine these elements in the advantageous manner taught only by applicants. Both references teach estrogen delivery systems. There is no reason to rearrange and combine elements to achieve the prevent invention. Applicants respectfully maintain that the claims as filed and amended are in condition for allowance.

CONCLUSION

If the Examiner has any questions or suggested Examiner's amendments, the Examiner is respectfully requested to call the undersigned.

The Commissioner is hereby authorized to charge any additional fees, or to credit any overpayment, to Deposit Account No. 50-3195.

Respectfully submitted,

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